REMARKS

Favorable reconsideration is earnestly solicited.

Claims 3-8, 10, 12, 15-17, 35-47, 55 and 57-63 are pending. Non-elected claims 5-8, 10, 12, 15-16, 35-47 and 55 were withdrawn from consideration by the Examiner. Claims 3-4, 17 and 57-63 are being examined and are under final rejection in the Office Action dated February 24, 2006.

Applicants thank the Examiner for considering the Information Disclosure Statement submitted on June 23, 2005 and for withdrawing some of the rejections.

Applicants moved "Cullin 3" and "CDC6" from claim 57 to claim 3 because those claims are identically worded except for recitation of those proteins, and claim 57 has a unique 35 U.S.C. 102 rejection related to the remaining protein tau. The amendment is believed to simplify issues for appeal and does not require additional search because the added limitation was already considered by the Examiner. The same remarks apply to the move of "Cullin 3" and "CDC6" from claim 59 to claim 17.

35 U.S.C. 112 – New Matter

Claims 3-4, 17 and 57-63 were rejected under Section 112, first paragraph, as being allegedly introducing "new matter." Applicants traverse.

Although Applicants disagree with the Examiner's allegation, the alleged "new matter" was removed from claims in order to further prosecution of this application.

Therefore, it is believed that the rejection is rendered moot by the amendment and withdrawal is requested.

35 U.S.C. 112 – Definiteness

Claims 3-4, 17 and 57-63 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Although Applicants disagree with the Examiner's allegation, the term "similarity" is replaced with the term "identity" (as suggested by the Examiner) in order to further prosecution of this application.

Therefore, it is believed that the rejection is rendered moot by the amendment and withdrawal is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 3-4, 17, 57 and 63 were rejected under Section 112, first paragraph, because it was alleged that the specification does not reasonably provide enablement for "isolated complexes comprising **derivatives of ubiquitin** with **fragments and derivatives of proteins** selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism." It was further alleged, "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." Applicants traverse.

A person skilled in the art would be able to practice the subject invention without undue experimentation in view of the disclosure in the specification and further in view of the high level of skill in the relevant art. The present specification clearly describes what Applicants regard as fragments and derivatives (or variants) in claiming their invention:

> The variants of the polypeptides according to the present invention may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, (ii) one in which there are one or more modified amino acid residues, e.g., residues that are modified by the attachment of substituent groups, (iii) one in which the polypeptide is an

> alternative splice variant of the polypeptide of the present invention, (iv) fragments of the polypeptides and/or (iv) one in which the polypeptide is fused with another polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification (for example, His-tag) or visualization (for example GFP). The fragments include polypeptides generated via proteolytic cleavage (including multi-site proteolysis) of an original sequence. Variants may be post-translationally, or chemically modified. Such variants are deemed to be within the scope of those skilled in the art from the teaching herein.

Specification at page 43, lines 9-22.

Further, many ubiquitin derivatives have been prepared and been shown to have activity in ubiquitylation reactions, see, e.g., the references in the Information Disclosure Statement submitted on June 23, 2005. A person skilled in the art would, therefore, have a significant amount of information available to guide them in making ubiquitin derivatives and assaying for their activities in accordance with Applicants' invention.

The "enablement" prong of Section 112, first paragraph, requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad descriptive terminology is of no importance. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Enablement is not precluded by the necessity for some experimentation such as routine screening, but the experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants urge that the experimentation required to practice the full scope of the pending claims is routine and not undue because a skilled artisan routinely engages in such experimentation.

With respect to N-end rule ubiquitylation of protein fragments, Applicants' specification provides numerous examples of ubiquitylated protein fragments of the claimed proteins as characterized by gel electrophoresis (see pages 41-42, providing molecular weight and cleavage position estimates for characterized protein fragments, Examples 2-6, and corresponding gel electrophoresis images in Figures 3-7).

The Office Action alleges on page 5 that there is unpredictability in the art with regard to the tertiary structure required for the interaction of substrate with the cognate E3 ubiquitin-protein ligase enzymes. Even assuming *arguendo* (i.e., without admission) that the Examiner's allegation is correct, Applicants urge that considerations of tertiary

structure are irrelevant to Applicants' invention because the specification discloses a high-throughput screening method routine in the art which will enable a skilled artisan to evaluate all variants and fragments of interest for the desired N-end rule ubiquitylation.

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and M.P.E.P. § 2164.06,
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> The test for enablement is whether one reasonably skilled in the art to make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988).

Further, the specification also teaches a skilled artisan, "The activity of these proteins as ubiquitylation substrates can be determined by measuring the accumulation of ubiquitylated products" (page 40, lines 11-13, and working examples on pages 76-89).

Applicants urge that any experimentation which may be required to practice their invention would be routine in the art. Therefore, the pending claims are enabled by the disclosure in the specification. Although Applicants disagree with the basis of the Examiner's rejection, claims 3, 5, 17, 57 and 59 are amended to recite further technical features of the claimed invention. Favorable reconsideration is earnestly solicited.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 3-4, 17 and 57-63 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse.

It appears that the Action asserts that the specification does not clearly describe the derivatives of ubiquitin and/or the fragments or derivatives of a protein. Applicants urge that the pending claims are clear in view of the disclosure in the specification and further in view of what is known in the art.

Applicants' specification discloses at page 32, "A person of ordinary skill in the art will recognize that the present invention relates not only to the specific protein sequences disclosed in the specification, but also to protein variants thereof such as fragments, analogs and/or derivatives." Moreover, the specification provides examples of what Applicants regard as protein variants on pages 43-45. Further, Applicants have amended the currently pending claims to replace term "similarity" with the term "identity" as suggested by the Examiner. The Information Disclosure Statement submitted on June 23, 2005 also provides specific references to derivatives of ubiquitin successfully tested in ubiquitylation reactions. And, furthermore, the specification provides methods for functionally testing the activity of these derivatives of ubiquitin and derivatives and fragments of proteins as ubiquitylation substrates by measuring the accumulation of ubiquitylated products (page 40, lines 11-13, and working examples on pages 76-89).

The pending claims require the complex between the protein and ubiquitin to be formed via a defined biological N-end rule pathway. This pathway imposes strict limits on the composition of matter and structurally restricts the final product (see specification at pages 4-5). In particular, there is a requirement in the pathway for an exposed destabilizing N-terminal residue. Applicants urge that in view of the limitation requiring ubiquitylation via the N-end rule pathway, the claims exclude non-functional fragments and derivatives that are not substrates of the pathway, thereby assuring that the breadth of claims are commensurate in scope with the disclosure.

Thus, the specification provides support for the presently claimed subject matter in compliance with the "written description" requirement of Section 112, first paragraph. The M.P.E.P. clearly states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.
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> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). **Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics** sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct.304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

M.P.E.P. § 2163(I), emphasis added.

It is improper to reject claims on the basis that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 USPQ 436, 437-38 (POBA 1974).

Although Applicants disagree with the basis of the Examiner's rejection, claims 3, 5, 17, 57 and 59 are amended to recite further technical features of the claimed invention. Favorable reconsideration is earnestly solicited.

35 U.S.C. 102 – Novelty

Claims 57-59 and 62-63 were rejected under Section 102(b) as allegedly anticipated by Morishima-Kawashima et al. (Neuron 10:1151-1160, 1993; hereinafter "Morishima-Kawashima"). Applicants traverse.

To clarify the technical issues, Applicants reanalyzed Table 1 from Morishima-Kawashima in view of the Examiner's comments in the Action and acknowledge that Table 1 does list fragments that resulted from a proteolytic cleavage of PHF smears. Applicants apologize for any confusion that their description of Table 1 might have caused. Morishima-Kawashima identified ubiquitylated N-terminally processed peptides of tau in pair-helical filaments as peptides that start with GDTP..., EAAGH... and PSSGE... (page 1156, left hand column). Applicants maintain their previous position that these peptide were not ubiquitylated by N-end rule ubiquitylation, however, even if they were ubiquitylated, the cited reference would not include all the limitations as set forth in the currently amended claims.

Applicants urge that the disclosure of Morishima-Kawashima does not anticipate claim 59. Claim 59 explicitly requires that the "complex is immobilized on a support and/or linked to a label." The complexes of the cited reference were extracted from the pair-helical filaments and are neither immobilized on support nor linked to a label. Consequently the disclosure of Morishima-Kawashima fails to teach or suggest at least one of the limitations of claim 59.

Further, Applicants urge that the disclosure of Morishima-Kawashima does not anticipate claim 57 (claims 58 and 63-63 are dependent of claim 57) as amended. Currently amended claim 57 is directed to a recombinant tau protein, as described in the specification on page 39 and in the "Materials and Methods" on pages 76-80 (e.g., "Protein was produced from the plasmid DNA in a transcription-translation reaction mixture," page 78, lines 25-26). The complexes of the cited reference were extracted from the brain and were not based on the recombinant tau, nor were they ubiquitilated in a reaction mixture. Consequently the disclosure of Morishima-Kawashima fails to teach or suggest at least one of the limitations of claim 57.

Applicants urge that as clearly stated in the M.P.E.P.:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

M.P.E.P. § 2131.

Morishima-Kawashima does not teach or suggest each and every element of claims 57-59 and 62-63. Thus, the rejection is improper and should be withdrawn.

Conclusion and Request for Interview

In view of the above, Applicants submit that the pending claims are in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, due to the large number of issues which were present in responding to this Office Action, Applicants believe that an interview would be helpful in addressing any issues which were not successfully traversed in this response or overcome by this response. Thus, Applicants respectfully request an interview with the Examiner once this response has been reviewed.

Respectfully submitted,

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